09/139425
AU #3

Set Items Description
? s protein(w)c(w)receptor

Processing
3251657 PROTEIN
2113814 C
1387233 RECEPTOR
S1 75 PROTEIN(W)C(W)RECEPTOR
? rd

...examined 50 records (50)
...completed examining records
S2 41 RD (unique items)
? t s2/3,ab/1-41

2/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11826329 BIOSIS NO.: 199900072438
Cloning and regulation of an endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%%.

AUTHOR: Fukudome K; Esmon C T
AUTHOR ADDRESS: Oklahoma City, Okla., USA

JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1217 (4):p3454 Dec. 22, 1998
ISSN: 0098-1133
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11441642 BIOSIS NO.: 199800222974
Activation mechanism of anticoagulant protein C in large blood vessels involving the endothelial cell %%%protein%%% %%%C%%% %%%receptor%%%.

AUTHOR: Fukudome Kenji(a); Ye Xiaofen; Tsuneyoshi Naoko; Tokunaga Osamu;
Sugawara Keishin; Mizokami Hiroshi; Kimoto Masao
AUTHOR ADDRESS: (a)Dep. Immunol., Saga Med. Sch., 5-1-1 Nabeshima, Saga 849
, Japan

JOURNAL: Journal of Experimental Medicine 187 (7):p1029-1035 April 6, 1998
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein C is an important regulatory mechanism of blood coagulation. Protein C functions as an anticoagulant when converted to the active serine protease form on the endothelial cell surface. Thrombomodulin (TM), an endothelial cell surface receptor specific for thrombin, has been identified as an essential component for protein C activation. Although protein C can be activated directly by the thrombin-TM complex, the conversion is known as a relatively low-affinity reaction. Therefore, protein C activation has been believed to occur only in microcirculation. On the other hand, we have identified and cloned a novel endothelial cell surface receptor (EPCR) that is capable of high-affinity binding of protein C and activated protein C. In this study, we demonstrate the constitutive, endothelial cell-specific expression of EPCR in vivo. Abundant expression was particularly detected in the aorta and large arteries. In vitro cultured, arterial endothelial cells were also found to express abundant EPCR and were capable of promoting significant levels of protein C activation. EPCR, was found to greatly accelerate protein C activation by examining functional activity in transfected cell lines expressing EPCR, and/or TM. EPCR decreased the dissociation constant and increased the maximum velocity for protein C activation mediated by the thrombin-TM complex. By these mechanisms, EPCR appears to enable significant levels of protein C activation in large vessels. These results suggest that the protein C anticoagulation pathway is important for the regulation of blood coagulation not only in microvessels but also in large vessels.

2/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11307378 BIOSIS NO.: 199800088710
Plasma levels of endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% are elevated in patients with sepsis and systemic lupus erythematosus: Lack of correlation with thrombomodulin suggests involvement of different pathological processes.

AUTHOR: Kurosawa Shinichiro(a); Stearns-Kurosawa D J(a); Carson Craig W;
D'Angelo Armando; Valle Patrizia Della; Esmon Charles T
AUTHOR ADDRESS: (a)Cardiovascular Biology Res., Okla. Med. Res. Foundation,
Oklahoma City, OK, USA

JOURNAL: Blood 91 (2):p725-727 Jan. 15, 1998
ISSN: 0006-4971
DOCUMENT TYPE: Letter; Article
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11285105 BIOSIS NO.: 199800066437
Cloning and in vitro analysis of the endothelial %%%protein%%% %%%C%%% %%%receptor%%% (EPCR) on human monocytes show that monocyte EPCR does not mediate the anti-inflammatory effects of activated protein C.

AUTHOR: Ahmad M F(a); Bach F H; Esmon C T; Hancock W W
AUTHOR ADDRESS: (a)Beth Israel Deaconess Med. Cent., Harvard Med. Sch.,
Boston, MA 02215, USA

JOURNAL: Blood 90 (10 SUPPL. 1 PART 1):p32A Nov. 15, 1997

CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology

ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11247779 BIOSIS NO.: 199800029111
Human %%%protein%%% %%%C%%% %%%receptor%%% is present primarily on endothelium of large blood vessels: Implications for the control of the protein C pathway.

AUTHOR: Laszik Zoltan; Mitro Alexander; Taylor Fletcher B Jr; Ferrell Gary; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma Med. Res. Foundation,
825 NE 13, Oklahoma City, OK 73104, USA

JOURNAL: Circulation 96 (10):p3633-3640 Nov. 18, 1997
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: The protein C anticoagulant pathway is critical to the control of hemostasis. Thrombomodulin and a newly identified receptor for protein C/activated protein C, EPCR, are both present on endothelium. EPCR augments activation of protein C by the thrombin-thrombomodulin complex. Methods and Results: To gain a better understanding of the relationship between thrombomodulin and EPCR, we compared the cellular specificity and tissue distributions of these two receptors by using immunohistochemistry. EPCR expression was detected almost exclusively on endothelium in human and baboon tissues. In most organs, EPCR was expressed relatively intensely on the endothelium of all arteries and veins, most arterioles, and some postcapillary venules. EPCR staining was usually negative on capillary endothelial cells. In contrast, thrombomodulin was detected at high concentrations in both large vessels and capillary endothelium. Both thrombomodulin and EPCR were expressed poorly on brain capillaries. The liver sinusoids were the only capillaries in which EPCR was expressed at moderate levels and thrombomodulin was low. EPCR and thrombomodulin were both expressed on
the endothelium of vasa recta in the renal medulla, the lymph node subcapsular and medullary sinuses, and some capillaries within the adrenal gland. Even in these organs the majority of capillaries were EPCR negative or stained weakly. Conclusions: These studies suggest that EPCR may be important in enhancing protein C activation on large vessels. The presence of high levels of EPCR on arterial vessels may help explain why partial protein C deficiency is a weak risk factor for arterial thrombosis.

2/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11239419 BIOSIS NO.: 199800020751
Functional characterization of 5'-flanking region of the mouse endothelial %%%protein%%% %%%C%%% %%%receptor%%% (EPCR) gene.

AUTHOR: Gu J M; Esmon C T
AUTHOR ADDRESS: Howard Hughes Med. Inst., Okla. Med. Res. Found., Oklahoma
City, OK 73104, USA

JOURNAL: Molecular Biology of the Cell 8 (SUPPL.):p228A Nov., 1997

CONFERENCE/MEETING: 37th Annual Meeting of the American Society for Cell
Biology Washington, D.C., USA December 13-17, 1997
SPONSOR: American Society for Cell Biology

ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11237187 BIOSIS NO.: 199800018519
The human %%%protein%%% %%%C%%% %%%receptor%%% is present primarily on
endothelium of large blood vessels: Implications for the control of the protein C pathway.

AUTHOR: Esmon Charles T(a); Laszik Zoltan; Mitro Alexander; Taylor Fletcher
B Jr; Ferrell Gary(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma City, OK, USA

JOURNAL: Circulation 96 (8 SUPPL.):pI604 10/21/97, 1997

CONFERENCE/MEETING: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

11233859 BIOSIS NO.: 199800015191
Soluble endothelial %%%protein%%% %%%C%%% %%%receptor%%% in human plasma.

AUTHOR: Kurosawa Shinichiro(a); Stearns-Kurosawa Deborah J(a); Hidari Noriko(a); Carson Craig W; Esmon Charles T
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Foundation, Oklahoma City, OK, USA

JOURNAL: Circulation 96 (8 SUPPL.):pI2 10/21/97, 1997

CONFERENCE/MEETING: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

11174614 BIOSIS NO.: 199799795759
The interaction between the endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% and protein C is dictated by the gamma-carboxyglutamic acid domain of protein C.

AUTHOR: Regan Lisa M; Mollica Jeffery S; Rezaie Alireza R; Esmon Charles T
(a)
AUTHOR ADDRESS: (a)Cardiovasc. Biol. Res. Program, Oklahoma Med. Res.
Foundation, 825 N. E. 13th St., Oklahoma City, USA

JOURNAL: Journal of Biological Chemistry 272 (42):p26279-26284 1997
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (EPCR)
binds to both protein C and activated protein C (APC) with similar affinity. Removal of the Gla domain of protein C results in the loss of most of the binding affinity. This observation is compatible with at least two models: 1) the Gla domain of protein C interacts with phospholipid on cell surfaces to stabilize interaction with EPCR or 2) the Gla domain of protein C makes specific protein-protein interactions with EPCR. The latter model predicts that chimeric proteins containing the protein C Gla domain should interact with EPCR. To test this, we constructed a prothrombin chimera in which the Gla domain and aromatic stack of prothrombin were replaced with the corresponding region of protein C. The 125I-labeled chimera (K-d = 176 nM) and 125I-APC (K-d = 65
nN) both bound specifically to 293 cells stably transfected with EPCR, but both bound poorly to sham-transfected cells. The chimera also blocked APC binding to EPCR-transfected cells in a dose-dependent fashion (K-i apprxeq 139 nM) similarly to protein C (K-i apprxeq 75 nM). Chimera binding to EPCR-transfected cells was blocked by soluble EPCR, demonstrating direct protein-protein interaction between the chimera and EPCR. Consistent with this conclusion, the isolated Gla domain of protein C -blocked APC binding to EPCR-transfected cells (IC-50 = 2 mu-M). No inhibition was observed with the isolated prothrombin Gla domain. A protein C chimera with the prothrombin Gla domain and aromatic stack failed to bind to EPCR detectably. These data suggest that the Gla domain of protein C is responsible for much of the binding energy and specificity of the protein C-EPCR interaction.

2/3,AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

11099125 BIOSIS NO.: 199799720270
Cloning of endothelial %%%protein%%% %%%C%%% %%%receptor%%% (EPCR) from

human monocytes.

AUTHOR: Ahmad M F(a); Storka D; Grey S; Bach F H; Esmon C T; Hancock W W
AUTHOR ADDRESS: (a)Beth Israel Deaconess Med. Cent., Harv. Med. Sch., Boston, MA 02215, USA

JOURNAL: FASEB Journal 11 (9):pA1166 1997

CONFERENCE/MEETING: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997
ISSN: 0892-6638
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11064593 BIOSIS NO.: 199799685738
Identification of functional endothelial %%%protein%%% %%%C%%% %%%receptor%%% in human plasma.

AUTHOR: Kurosawa Shinichiro; Stearns-Kurosawa Deborah J; Hidari Noriko; Esmon Charles T(a)
AUTHOR ADDRESS: (a)825 N.E. 13th St., Oklahoma City, OK 73104, USA

JOURNAL: Journal of Clinical Investigation 100 (2):p411-418 1997
ISSN: 0021-9738
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (EPCR)
binds protein C and facilitates activation by the thrombin-thrombomodulin complex. EPCR also binds activated protein C (APC) and inhibits APC anticoagulant activity. In this study, we detected a soluble form of EPCR in normal human plasma. Plasma EPCR appears to be apprx 43,000 D, and circulates at apprx 100 ng/ml (98.4+-27.8 ng/ml, n = 22). Plasma EPCR was purified from human citrated plasma using ion exchange, immunoaffinity, and protein C affinity chromatography. Flow cytometry experiments demonstrated that plasma EPCR bound APC with an affinity similar to that previously determined for recombinant soluble EPCR (K-dapp = 30 nM). Furthermore, plasma EPCR inhibited both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage Factor Xa clotting assay. The physiological function of plasma EPCR is uncertain, but if the local concentrations are sufficiently high, particularly in disease states, the present data suggest that the soluble plasma EPCR could attenuate the membrane-bound EPCR augmentation of protein C activation and the anticoagulant function of APC.

2/3,AB/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

11032291 BIOSIS NO.: 199799653436
The protein C pathway: New insights.

AUTHOR: Esmon Charles T(a); Ding Wei; Yasuhiro Katsuura; Gu Jian-Ming; Ferrell Gary; Regan Lisa M; Stearns-Kurosawa Deborah J; Kurosawa Shimichiro; Mather Timothy; Laszik Zolton; Esmon Naomi L
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma Med. Res. Foundation, 825 NE 13, Oklahoma City, OK 73104, USA

JOURNAL: Thrombosis and Haemostasis 78 (1):p70-74 1997
ISSN: 0340-6245
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

10910910 BIOSIS NO.: 199799532055
Increased expression of the endothelial cell %%%protein%%% %%%c%%% %%%receptor%%% in multidrug resistant tumor cells.

AUTHOR: Scheffer G L(a); Flens M J; Hageman S; Lawry J; Izquierdo M A; Clevers H C; Slovak M L; Shoemaker R H; Van Der Valk P; Scheper R J
AUTHOR ADDRESS: (a)Dep. Pathol., Free Univ. Hosp., Amsterdam, Netherlands

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 38 (0):p396 1997

CONFERENCE/MEETING: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10684158 BIOSIS NO.: 199799305303
Upregulation of the message for rodent endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (EPCR) by endotoxin and thrombin.

AUTHOR: Ding Wei(a); Gu Jian-Ming; Fukudome Kenji; Laszik Zoltan; Grammas Paula; Esmon Charles T
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Fdn., Oklahoma City, OK, USA

JOURNAL: Circulation 94 (8 SUPPL.):pI694 1996

CONFERENCE/MEETING: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

10684157 BIOSIS NO.: 199799305302
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% participates in protein C activation.

AUTHOR: Kurosawa Shinichiro(a); Fukudome Kenji; Stearns-Kurosawa Debbie; Mollica Jeff; Ferrell Gary; Hidari Noriko; Esmon Charles T
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Fdn., Oklahoma City, OK, USA

JOURNAL: Circulation 94 (8 SUPPL.):pI694 1996

CONFERENCE/MEETING: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10574195 BIOSIS NO.: 199699195340
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% augments protein C activation by the thrombin-thrombomodulin complex.

AUTHOR: Stearns-Kurosawa Deborah J; Kurosawa Shinichiro; Mollica Jeffery S;

Ferrell Gary L; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst. Res. Lab., Acree-Woodworth Res.
Building, 820 NE 15, Room A205, Oklahom, USA

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 93 (19):p10212-10216 1996
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein C activation on the surface of the endothelium is critical to the negative regulation of blood coagulation. We now demonstrate that monoclonal antibodies that block protein C binding to the endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (EPCR) reduce protein C activation rates by the thrombin-thrombomodulin complex on endothelium, but that antibodies that bind to EPCR without blocking protein C binding have no effect. The kinetic result of blocking the EPCR-protein C interaction is an increased apparent K-m for the activation without altering the affinity of thrombin for thrombomodulin. Activation rates of the protein C derivative lacking the gamma-carboxyglutamic acid domain, which is required for binding to EPCR, are not altered by the anti-EPCR antibodies. These data indicate that the protein C activation complex involves protein C, thrombin, thrombomodulin, and EPCR. These observations open new questions about the control of coagulation reactions on vascular endothelium.

2/3,AB/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10478349 BIOSIS NO.: 199699099494
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%%: Cell surface expression and direct ligand binding by the soluble receptor.

AUTHOR: Fukudome Kenji; Kurosawa Shinichiro; Stearns-Kurosawa Deborah J; He Xuhua; Rezaie Alireza R; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Foundation, Cardiovascular Biol.
Res., 825 N.E. 13th St., Oklahoma City, OK 7, USA

JOURNAL: Journal of Biological Chemistry 271 (29):p17491-17498 1996
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Expression of the endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (EPCR) gene in mammalian cells imparts the capacity to bind activated protein C (APC) or protein C. Immunochemical analysis of CCD41, apparently the murine homologue of EPCR, suggested centrosomal localization, raising questions about the location of the EPCR gene product and its role in protein C binding. In this study, we express a soluble form of EPCR, demonstrate EPCR expression on the cell surface, and direct binding between soluble EPCR and protein C/APC. Affinity purified polyclonal and a monoclonal antibody against EPCR bound to the cell surface of EPCR-transfected cells but not to control cells. A 49-kDa protein, a mass similar to soluble EPCR, was immunoprecipitated from the cell surface of endothelium and cells transfected with human EPCR but not from control cells. The FLAG antibody and APC bound to cells expressing an EPCR construct containing the FLAG epitope located in a putative extracellular domain, whereas an EPCR construct truncated just before the putative transmembrane domain produced only soluble EPCR antigen. Soluble EPCR inhibited APC binding to EPCR expressing cells in a concentration-dependent fashion, K-d(app) = 29 nM and bound to immobilized protein C in a Ca-2+-dependent fashion. Thus, EPCR is a type I transmembrane protein that binds directly to APC.

2/3,AB/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10477211 BIOSIS NO.: 199699098356
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%%: Inhibition of activated protein C anticoagulant function without modulation of reaction with proteinase inhibitors.

AUTHOR: Regan Lisa M; Stearns-Kurosawa Deborah J; Kurosawa Shinichiro; Mollica Jeff; Fukudome Kenji; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Foundation, Cardiovascular Biol.
Res., 825 N.E. 13th St., Oklahoma City, OK 7, USA

JOURNAL: Journal of Biological Chemistry 271 (29):p17499-17503 1996
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A soluble form of the endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (EPCR) was analyzed for the ability to modulate the functional properties of protein C and activated protein C (APC). In a plasma clotting system initiated with factor Xa, EPCR blocked the anticoagulant activity of APC in a dose-dependent fashion. EPCR had no influence on clotting in the absence of APC. Consistent with the plasma results, EPCR slowed the proteolytic inactivation of factor Va by slowing both of the key proteolytic cleavages in the heavy chain of factor Va. EPCR did not prevent protein C activation by the soluble thrombinthrombomodulin complex, did not alter the inactivation of APC by alpha-1-antitrypsin or protein C inhibitor, and did not influence the kinetics of peptide paranitroanilide substrate cleavage significantly. We conclude that EPCR binds to an exosite on APC that selectively modulates the enzyme specificity in a manner reminiscent of the influence of thrombomodulin on thrombin.

2/3,AB/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10288691 BIOSIS NO.: 199698743609
The Gla-26 residue of protein C is required for the binding of protein C to thrombomodulin and endothelial cell %%%protein%%% %%%C%%% %%%receptor%%%, but not protein S and factor Va.

AUTHOR: Nishioka Junji; Ido Masaru; Hayashi Tatsuya; Suzuki Koji(a)
AUTHOR ADDRESS: (a)Dep. Mol. Pathobiol., Mie Univ. Sch. Med., Tsu-city, Mie
514, Japan

JOURNAL: Thrombosis and Haemostasis 75 (2):p275-282 1996
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A functionally defective protein C (PC)-Mie, detected in the plasma of a patient with hereditary thrombophilia, has Lys substituted for gamma-carboxyglutamic acid (Gla)-26 residue. The activation rate of PC-Mie by Protac or thrombin in the absence of Ca-2+ and that by thrombin with native thrombomodulin (TM), recombinant soluble truncated TM or on cultured endothelial cells in the presence of Ca-2+ were all apparently lower than that of normal PC. The anticoagulant activity of Protac-activated PC (APC)-Mie on the plasma clotting time and the rate of inactivation of factor Va by APC-Mie in the presence of phospholipids were lower than those seen with normal APC. APC-Mie and normal APC bound equally to protein S and to biotinyl-factor Va. However, neither PC-Mie nor APC-Mie bound to phospholipids and to cultured human endothelial cells. It was similar to that observed with Gla-domainless PC/APC, but different from that seen with normal PC/APC. These results suggest that Gla-26-dependent conformation is required for the binding of PC/APC to phospholipids, TM and the surface of endothelial cell PC/APC receptor, but not to protein S and factor Va.

2/3,AB/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10165690 BIOSIS NO.: 199698620608
Evidence for a free sulfhydryl (S) in the endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%% (EPCR).

AUTHOR: Regan L; Rezaie A R; Fukudome K; Stearns-Kurosawa D J; Kurosawa S;
Mollica J; Esmon C T
AUTHOR ADDRESS: Cardiovascular Biology, Okla. Med. Res. Foundation, Howard
Hughes Med. Inst., Oklahoma City, OK, USA

JOURNAL: Blood 86 (10 SUPPL. 1):p197A 1995

CONFERENCE/MEETING: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10165689 BIOSIS NO.: 199698620607
Cell surface expression of the endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%% (EPCR).

AUTHOR: Fukudome K; Kurosawa S; Stearns-Kurosawa D J; Regan L; Esmon C T
AUTHOR ADDRESS: Cardiovascular Biology, Okla. Med. Res. Foundation, Oklahoma City, OK, USA

JOURNAL: Blood 86 (10 SUPPL. 1):p197A 1995

CONFERENCE/MEETING: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09765091 BIOSIS NO.: 199598220009
Molecular cloning and expression of murine and bovine endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%% (EPCR): The
structural and functional conservation in human, bovine and murine EPCR.

AUTHOR: Fukudome Kenji; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma Med. Res. Found., 825
NE 13, Oklahoma City, OK 73104, USA

JOURNAL: Journal of Biological Chemistry 270 (10):p5571-5577 1995
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recently, we identified and cloned a human endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%% (EPCR). EPCR was
predicted to be a type 1 transmembrane glycoprotein and a novel member of the CD1/major histocompatibility complex superfamily with 28% identity with CD1d. Even greater homology (62% identity) was detected with the murine protein, CCD41, which was previously characterized as a centrosome-associated, cell cycle-dependent protein. This raised the possibility that CCD41 was the murine homologue of EPCR. To address this possibility, to better understand structure-function relationships, and to facilitate physiological experiments on EPCR function, we cloned and sequenced murine and bovine EPCR from endothelial cell cDNA libraries. The nucleotide sequence of murine EPCR and CCD41 exhibited five differences corresponding to one base change, three single-base insertions, and one base deletion in the protein coding region. As a result, the predicted structures of EPCR and CCD41 differed in their amino and carboxyl termini but were identical in the central portion of the coding sequence. Based on comparison of the murine, bovine, and human EPCR sequences and the regions where discrepancies between murine EPCR and CCD41 were detected, we believe that CCD41 is probably identical to murine EPCR and that the reported sequence differences are likely the result of compression on the sequencing gel. Compared with human EPCR, the murine and bovine sequences were 69 and 73% identical, respectively, and 57% of the residues were identical between all three species. Both bovine and murine EPCR could bind human activated protein C when the cDNA
clones were transfected into 293T cells. Like human EPCR, of the cell lines tested, the murine EPCR message was restricted to endothelium. Cloning of the murine and bovine homologue of EPCR will facilitate in vivo and in vitro studies of the role of EPCR in the protein C pathway.

2/3,AB/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09566951 BIOSIS NO.: 199598021869
Identification, cloning and regulation of a novel endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%%.

AUTHOR: Fukudome Kenji; Esmon Charles T
AUTHOR ADDRESS: Howard Hughes Med. Inst., Cardiovascular Program, Oklahoma
Med. Res. Foundation, Oklahoma City, OK, USA

JOURNAL: Circulation 90 (4 PART 2):pI133 1994

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ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

2/3,AB/24 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07155069 EMBASE No: 1998037482
Plasma levels of endothelial cell %%%protein%%% %%%C%%% %%%receptor%%%
are elevated in patients with sepsis and systemic lupus erythematosus: Lack of correlation with thrombomodulin suggests involvement of different pathological processes (3)

Kurosawa S.; Stearns-Kurosawa D.J.; Carson C.W.; D'Angelo A.; Della Valle P.; Esmon C.T.
S. Kurosawa, Cardiovascular Biology Research, Oklahoma Medical Research Foundation, Oklahoma City, OK United States

Blood (BLOOD) (United States) 1998, 91/2 (725-727)

CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Letter
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 12

2/3,AB/25 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06422492 EMBASE No: 1996085709
The Glasup 2sup 6 residue of protein C is required for the binding of protein C to thrombomodulin and endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%%, but not to protein S and factor Va

Nishioka J.; Ido M.; Hayashi T.; Suzuki K.
Department of Molecular Pathobiology, Mie University School of Medicine,Tsu-city, Mie 514 Japan

Thrombosis and Haemostasis (THROMB. HAEMOST.) (Germany) 1996, 75/2
(275-282)

CODEN: THHAD ISSN: 0340-6245
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

A functionally defective protein C (PC)-Mie, detected in the plasma of a patient with hereditary thrombophilia, has Lys substituted for gamma-carboxyglutamic acid (Gla)sup 2sup 6 residue. The activation rate of PC-Mie by Protac or thrombin in the absence of Casup 2sup + and that by thrombin with native thrombomodulin (TM), recombinant soluble truncated TM
or on cultured endothelial cells in the presence of Casup 2sup + were all apparently lower than that of normal PC. The anticoagulant activity of Protac-activated PC (APC)-Mie on the plasma clotting time and the rate of inactivation of factor Va by APC-Mie in the presence of phospholipids were lower than those seen with normal APC, APC-Mie and normal APC bound equally
to protein S and to biotinyl-factor Va. However, neither PC-Mie nor APC-Mie bound to phospholipids and to cultured human endothelial cells. It was similar to that observed with Gla-domainless PC/APC, but different from that seen with normal PC/APC. These results suggest that Glasup 2sup 6-dependent conformation is required for the binding of PC/APC to phospholipids, TM and the surface of endothelial cell PC/APC receptor, but not to protein S and factor Va.

2/3,AB/26 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09886186 99156958
Reconstitution of the human endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%% with thrombomodulin in phosphatidylcholine vesicles enhances
protein C activation.
Xu J; Esmon NL; Esmon CT
Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104, USA.
J Biol Chem (UNITED STATES) Mar 5 1999, 274 (10) p6704-10, ISSN
0021-9258 Journal Code: HIV
Contract/Grant No.: P01 HL54804, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Blocking protein C binding to the endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%% (EPCR) on the endothelium is known to reduce protein C
activation rates. Now we isolate human EPCR and thrombomodulin (TM) and
reconstitute them into phosphatidylcholine vesicles. The EPCR increases protein C activation rates in a concentration-dependent fashion that does not saturate at 14 EPCR molecules/TM. Without EPCR, the protein C concentration dependence fits a single class of sites (Km = 2.17 +/- 0.13 microM). With EPCR, two classes of sites are apparent (Km = 20 +/- 15 nM and Km = 3.2 +/- 1.7 microM). Increasing the EPCR concentration at a constant TM concentration increases the percentage of high affinity sites. Holding the TM:EPCR ratio constant while decreasing the density of these proteins results in a decrease in the EPCR enhancement of protein C activation, suggesting that there is little affinity of the EPCR for TM. Negatively charged phospholipids also enhance protein C activation. EPCR acceleration of protein C activation is blocked by anti-EPCR antibodies, but not by annexin V, whereas the reverse is true with negatively charged phospholipids. Human umbilical cord endothelium expresses approximately 7 times more EPCR than TM. Anti-EPCR antibody reduces protein C activation
rates 7-fold over these cells, whereas annexin V is ineffective, indicating that EPCR rather than negatively charged phospholipid provide the surface for protein C activation. EPCR expression varies dramatically among vascular beds. The present results indicate that the EPCR concentration will determine the effectiveness of the protein C activation complex.

2/3,AB/27 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09648038 98316433
Changes of resistance to activated protein C in the course of pregnancy and prevalence of factor V mutation.
Mimuro S; Lahoud R; Beutler L; Trudinger B
Department of Obstetrics and Gynaecology, University of Sydney at Westmead Hospital, New South Wales, Australia.
Aust N Z J Obstet Gynaecol (AUSTRALIA) May 1998, 38 (2) p200-4, ISSN
0004-8666 Journal Code: 910
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The purpose of this study was to examine the changes in activated protein C (APC) anticoagulant activity during pregnancy and determine whether changes in APC could contribute to thrombosis in the placental bed in preeclampsia. We measured APC anticoagulant activity in 150 women with a normal pregnancy and 50 women with preeclampsia. There was a significant reduction in the mean APC sensitivity ratio (APC-SR) during pregnancy ($p<0.001$). APC resistance in preeclampsia was significantly higher than in normal pregnancy ($p<0.01$). Amongst women with APC resistance the presence
of the factor V Leiden mutation was significantly higher in the preeclampsia group than in the normal pregnancy group ($p<0.01$). It seems that both factor V Leiden mutation and APC resistance may be associated with the development of preeclampsia. These results suggest that APC resistance may be an important mechanism underlying placental bed pathology in pregnancy and may be associated with an increased tendency to develop preeclampsia in some women. Assay of APC resistance and factor V Leiden mutation should be performed in women with preeclampsia.

2/3,AB/28 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09324231 98001978
[Recurrent thrombophlebitis and ulcera crurum as manifestations of hereditary blood coagulation disorders and Klinefelter syndrome. Discussion based on 4 case examples]
Rezidivierende Phlebothrombosen und Ulcera crurum als Manifestationsformen hereditarer Gerinnungsstorungen und des Klinefelter-Syndroms. Diskussion anhand von 4 Fallbeispielen.
Ramaker J; Goerdt S; Zouboulis CC; Schramm W; Orfanos CE
Hautklinik und Poliklinik, Universitatsklinikum Benjamin Franklin, Freie Universitat, Berlin.
Hautarzt (GERMANY) Sep 1997, 48 (9) p634-9, ISSN 0017-8470 Journal Code: G13
Languages: GERMAN Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE English Abstract
Recurrent phlebothromboses in young patients with subsequent severe postthrombotic syndrome and chronic venous leg ulcers may be caused by underlying hereditary disorders of hemostasis or may occur as part of other congenital syndromes. The most common hereditary disorders of hemostasis in this respect appear to be deficiencies of antithrombin III, protein C, and protein S, and activated protein C resistance (mutations of factor V). Less frequently, dysfibrinogenemia, increased plasminogen activator inhibitor levels, or deficiencies of tissue plasminogen activator or heparin cofactor II may be found. Klinefelter's syndrome and homocystinuria are prime examples of those rare congenital disorders indirectly associated with an elevated risk of thrombosis in young individuals. Early diagnosis of these disorders will allow timely treatment, preventive care and counselling of patients as well as family members.

2/3,AB/29 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09324141 98002034
[Screening in activated protein C resistance]
Screening bei APC-Resistenz.
Bergmann F
Abteilung Hamatologie/Onkologie, Kinderklinik der Medizinischen Hochschule Hannover.
Internist (Berl) (GERMANY) Sep 1997, 38 (9) p864, ISSN 0020-9554 Journal Code: GVX
Languages: GERMAN
Document type: JOURNAL ARTICLE

2/3,AB/30 (Item 5 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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08944717 97054867
Use of the direct RNA amplification technique NASBA to detect factor V Leiden, a point mutation associated with APC resistance.
Reitsma PH; van der Velden PA; Vogels E; van Strijp D; Tacken N; Adriaansen H; van Gemen B
Department of Hematology, University Hospital, Leiden, The Netherlands.
Blood Coagul Fibrinolysis (ENGLAND) Sep 1996, 7 (6) p659-63, ISSN 0957-5235 Journal Code: A5J
Languages: ENGLISH
Document type: JOURNAL ARTICLE
APC resistance is a common and strong hereditary risk factor for venous thrombosis. This plasma abnormality appears to be almost always caused by the same defect in the coagulation factor V gene (a G --> A transition at nucleotide 1691 leading to replacement of 506 Arg by Gln; factor V Leiden). Therefore, it is possible to consider a simple and specific genetic test as an alternative to a plasma APC resistance test that is compromised by treatment and other factors. We have investigated whether a new amplification procedure, NASBA, together with the detection procedure ELGA
would provide a simple protocol for the nucleotide specific detection of the factor V mutation.

2/3,AB/31 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08944710 97054858
Homozygous patients with APC resistance may remain paucisymptomatic or asymptomatic during oral contraception.
Girolami A; Simioni P; Girolami B; Radossi P
Institute of Medical Semiotics, University of Padua Medical School, Italy.
Blood Coagul Fibrinolysis (ENGLAND) Sep 1996, 7 (6) p590-4, ISSN 0957-5235 Journal Code: A5J
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effect of oral contraceptive therapy was studied in five patients with homozygous activated protein C resistance. Patients with this congenital abnormality, in contrast to those with antithrombin, protein C or protein S deficiencies, showed only a mild thrombotic tendency. In fact, only two of six observations (one patient took the pill on two separate occasions many years apart) showed deep vein thrombosis. No patient had pulmonary embolism. Two additional patients had a superficial vein thrombosis of the legs. In two instances, a superficial vein thrombosis and a deep vein thrombosis, concomitant risk factors were present (immobilization and surgery for an ovarian cyst, respectively). However, compared with heterozygous for the same abnormality, the symptomatic homozygous patients with APC resistance appeared to develop thrombosis after a shorter period of oral contraception.

2/3,AB/32 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

08924498 97079941
Thrombotic tendency in 75 symptomatic, unrelated patients with APC resistance.
Melichart M; Kyrle PA; Eichinger S; Rintelen C; Mannhalter C; Pabinger I
First Department of Medicine, University of Vienna.
Wien Klin Wochenschr (AUSTRIA) 1996, 108 (19) p607-10, ISSN 0043-5325
Journal Code: XOP
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Resistance to activated protein C (APC resistance) was measured in 284 individuals (169 females, 115 males) with a history of objectively confirmed venous thrombosis and/or pulmonary embolism. A decreased APC
resistance ratio was found in 75 patients (26%), 47 were females, 28 males. Factor V Leiden was investigated in 60 of 75 patients with APC resistance, of whom 46 were heterozygous, 4 homozygous. In 10 APC resistant patients the Arg 506 Glu mutation was not identified. The median age of the first thromboembolic event in patients with APC resistance was 42 years (range 15-82 years). Most patients had a history of deep vein thrombosis (83%), 28% had experienced pulmonary embolism. More unusual sites of thrombosis were the deep arm veins (7%) and mesenteric veins (one patient, 1.3%). 53% of patients developed the first thromboembolic event spontaneously. Precipitating conditions for thromboembolism were surgery in 9.3% and trauma in 8%. In one third of female patients the first thromboembolic event occurred in conjunction with pregnancy and delivery (14.8%) or oral contraceptives (19%). At the time of investigation 40% of patients with APC resistance had experienced recurrent thromboembolic events. The family history was positive in 60% of patients. We conclude that the clinical feature of APC resistance is similar to the feature of a deficiency of antithrombin, protein C and protein S. Pregnancy, delivery and oral contraceptives seem to be a relevant additional risk factors for thrombosis in females with APC resistance.

2/3,AB/33 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

08924497 97079940
[Activated protein C resistance--an evaluation of current status (see comments)]
Aktivierte Protein C-Resistenz--eine Standortbestimmung.
Hopmeier P
Krankenanstalt Rudolfstiftung, Wien.
Wien Klin Wochenschr (AUSTRIA) 1996, 108 (19) p599-606, ISSN 0043-5325 Journal Code: XOP
Comment in Wien Klin Wochenschr 1996;108(19):595-8
Languages: GERMAN Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English
Abstract
The discovery of APC resistance and of the factor V Leiden mutation brought a break-through in thrombosis research and has greatly improved our understanding of the pathogenesis of venous thrombosis. In particular, it became obvious that thrombotic disease is the result of multiple factors. However, many clinically relevant questions still remain unanswered: for instance, the individual risk of thrombosis for a gene carrier is difficult to assess, since only some of the factors which may finally lead to thrombosis are presently recognized as such. The functional tests which are in common use today have a number of drawbacks and will soon be replaced by improved methods.

2/3,AB/34 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08521348 96124295
Cellular regulation of the protein C pathway.
Esmon CT; Fukudome K
Oklahoma Medical Research Foundation, Department of Pathology, University
of Oklahoma Health Sciences Center, Oklahoma City 73104, USA.
Semin Cell Biol (UNITED STATES) Oct 1995, 6 (5) p259-68, ISSN 1043-4682 Journal Code: A60
Contract/Grant No.: R37 HL30340, HL, NHLBI; R01 HL 29807, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The protein C anticoagulant pathway regulates thrombin formation. The pathway is triggered when thrombin binds to the endothelial cell proteoglycan, thrombomodulin. Unlike thrombin, this complex is a potent activator of the protein C zymogen, but it cannot clot blood. Activated protein C binds to protein S on cell surfaces where it proteolytically inactivates coagulation factors Va and VIIIa. Activated protein C also binds to a newly identified endothelial %%%protein%%% %%%C%%%
%%%receptor%%%. Congenital deficiencies in this pathway are associated with
thrombotic disease, and inflammation can cause acquired deficiencies. Activated protein C appears to inhibit inflammation. Thus, this pathway modulates both coagulation and inflammation.

2/3,AB/35 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08295016 95234783

Erroneously low APC ratio in patients with lupus anticoagulant [letter]
Gschwandtner ME; Lechner K; Pabinger I
Ann Hematol (GERMANY) Mar 1995, 70 (3) p169-70, ISSN 0939-5555
Journal Code: A2P
Languages: ENGLISH
Document type: LETTER

2/3,AB/36 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08116299 95159086
High affinity binding sites for activated protein C and protein C on cultured human umbilical vein endothelial cells. Independent of protein S and distinct from known ligands.
Bangalore N; Drohan WN; Orthner CL
Plasma Derivatives Laboratory, American Red Cross Holland Laboratory, Rockville, Maryland 20855.
Thromb Haemost (GERMANY) Sep 1994, 72 (3) p465-74, ISSN 0340-6245
Journal Code: VQ7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Activated protein C (APC) is an antithrombotic serine proteinase having anticoagulant, profibrinolytic and anti-inflammatory activities. Despite its potential clinical utility, relatively little is known about its clearance mechanisms. In the present study we have characterized the interaction of APC and its active site blocked forms with human umbilical vein endothelial cells (HUVEC). At 4 degrees C 125I-APC bound to HUVEC in a
specific, time dependent, saturable and reversible manner. Scatchard analysis of the binding isotherm demonstrated a Kd value of 6.8 nM and total number of binding sites per cell of 359,000. Similar binding isotherms were obtained using radiolabeled protein C (PC) zymogen as well as D-phe-pro-arg-chloromethylketone (PPACK) inhibited APC indicating that a functional active site was not required. Competition studies showed that the binding of APC, PPACK-APC and PC were mutually exclusive suggesting
that they bound to the same site(s). Proteolytic removal of the N-terminal gamma-carboxyglutamic acid (gla) domain of PC abolished its ability to compete indicating that the gla-domain was essential for cell binding. Surprisingly, APC binding to these cells appeared to be independent of protein S, a cofactor of APC generally thought to be required for its high affinity binding to cell surfaces. The identity of the cell binding site(s), for the most part, appeared to be distinct from other known APC ligands which are associated with cell membranes or extracellular matrix including phospholipid, thrombomodulin, factor V, plasminogen activator inhibitor type 1 (PAI-1) and heparin. Pretreatment of HUVEC with antifactor VIII antibody caused partial inhibition of 125I-APC binding indicating that factor VIII or a homolog accounted for approximately 30% of APC binding. Studies of the properties of surface bound 125I-APC or 125I-PC and their fate at 4 degrees C compared to 37 degrees C were consistent with association of approximately 25% of the initially bound radioligand with an endocytic receptor. However, most of the radioligand appeared not to be bound to an endocytic receptor and dissociated rapidly at 37 degrees C in an intact and functional state. These data indicate the presence of specific, high affinity binding sites for APC and PC on the surface of HUVEC. While a minor proportion of binding sites may be involved in endocytosis, the identity and function of the major proportion is presently unknown. It is speculated that this putative receptor may be a further mechanisms of localizing the PC antithrombitic system to the vascular endothelium.

2/3,AB/37 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0226101 DBA Accession No.: 98-07698 PATENT
Regulatory elements from the endothelial %%%protein%%%-%%%C%%% %%%receptor%%% promoter - vector-mediated ribozyme, antisense, triple helix oligonucleotide, RNA-ase-P guiding molecule or gene transfer to vascular endothelium cells
AUTHOR: Esmon C T; Gu J M
CORPORATE SOURCE: Oklahoma City, OK, USA.
PATENT ASSIGNEE: Oklahoma-Med.Res.Found. 1998
PATENT NUMBER: WO 9820041 PATENT DATE: 980514 WPI ACCESSION NO.:
98-286871 (9825)
PRIORITY APPLIC. NO.: US 54533 APPLIC. DATE: 970804
NATIONAL APPLIC. NO.: WO 97US20364 APPLIC. DATE: 971107
LANGUAGE: English
ABSTRACT: New regulatory elements (I) (DNA sequence specified) from
endothelium %%%protein%%%-%%%C%%% %%%receptor%%% (EPCR) promoter may be
inducible by exposure to serum, or direct expression selectively to endothelium cells, or to large vessel endothelium cells. Also claimed are constructs for heterologous gene expression containing (I) and optionally a recombinant gene and/or a thrombin response element. (I) are useful to control expression of a gene or biologically active molecule, either specifically in endothelium cells and/or as a result of environmental stimuli e.g. thrombin or serum. (I) are particularly useful in gene therapy of atherosclerosis and most other vascular diseases, when the construct contains a therapeutic gene, a ribozyme, antisense or triple helix oligonucleotides or guide sequences for RNA-ase-P which are used to mutate or stop transcription of a particular gene. (I) are also useful as DNA probes, in increasing expression of recombinant proteins by exposure of the encoding construct to thrombin and in drug screening and design. (69pp)

2/3,AB/38 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0194874 DBA Accession No.: 96-05645 PATENT
Isolated endothelial cell protein-C/activated %%%protein%%%-%%%C%%% %%%receptor%%% - gene cloning and expression for use as an antiinflammatory or anticoagulant; inhibitory nucleic acid for use in cancer therapy; antitumor receptor-antagonist isolation
AUTHOR: Fukudome K; Esmon C T
CORPORATE SOURCE: Oklahoma City, OK, USA.
PATENT ASSIGNEE: Oklahoma-Med.Res.Found. 1996
PATENT NUMBER: WO 9605303 PATENT DATE: 960222 WPI ACCESSION NO.:
96-139699 (9614)
PRIORITY APPLIC. NO.: US 289699 APPLIC. DATE: 940812
NATIONAL APPLIC. NO.: WO 95US9636 APPLIC. DATE: 950809
LANGUAGE: English
ABSTRACT: A new isolated human endothelial cell protein-C-activated-%%%protein%%%-%%%C%%% %%%receptor%%% has a specified DNA sequence or
derivative, and may be expressed on the surface of a non-human cell or non-endothelial cell, or may be in soluble form (lacking at least part of the transmembrane region). The DNA may be inserted in a vector for expression in a host cell. An inflammatory response may be enhanced by blocking binding of protein-C (EC-3.4.21.69) or activated protein-C to the receptor using an antibody or fragment, inhibitory nucleic acid or other types of compound. An inflammatory response may be inhibited using the receptor or an agonist. These antiinflammatory compounds may be useful in therapy of e.g. Gram-negative bacterium sepsis, apoplexy, thrombosis, septic shock, acute respiratory distress syndrome or pulmonary embolism. Localization of the receptor to surfaces in contact with blood renders the surfaces anticoagulant by concentration of activated protein-C, so may be used in coating of vascular grafts. Receptor-antagonists may be useful as e.g. antitumor agents. (58pp)

2/3,AB/39 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

129213853 CA: 129(17)213853z PATENT
Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor
INVENTOR(AUTHOR): Esmon, Charles T.; Stearns-Kurosawa, Deborah J.; Kurosawa, Shinichiro
LOCATION: USA
ASSIGNEE: Oklahoma Medical Research Foundation
PATENT: United States ; US 5804392 A DATE: 19980908
APPLICATION: US 884203 (19970627)
PAGES: 23 pp. CODEN: USXXAM LANGUAGE: English CLASS: 435007100;
G01N-033/53A; G01N-033/564B; C07K-016/28B

2/3,AB/40 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

129024180 CA: 129(3)24180s PATENT
The promoter region of the endothelial protein C receptor gene and its use in endothelium-specific expression
INVENTOR(AUTHOR): Esmon, Charles T.; Gu, Jian-ming
LOCATION: USA
ASSIGNEE: Oklahoma Medical Research Foundation
PATENT: PCT International ; WO 9820041 A1 DATE: 19980514
APPLICATION: WO 97US20364 (19971107) *US 30718 (19961108) *US 54533
(19970804)
PAGES: 28 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-014/705A
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK
; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

2/3,AB/41 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

125001378 CA: 125(1)1378r PATENT
Cloning and regulation of an endothelial cell protein C receptor and use for inflammation regulation
INVENTOR(AUTHOR): Fukudome, Kenji; Esmon, Charles T.
LOCATION: USA
ASSIGNEE: Oklahoma Medical Research Foundation
PATENT: PCT International ; WO 9605303 A1 DATE: 960222
APPLICATION: WO 95US9636 (950809) *US 289699 (940812)
PAGES: 57 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/12A;
C07K-014/705B; A61K-039/395B; C12N-015/11B; A61K-038/17B; C07K-016/28B;
G01N-033/68B DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE
; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
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FILE 'USPAT' ENTERED AT 11:37:29 ON 28 APR 1999

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*  WELCOME TO THE  *
*  U.S. PATENT TEXT FILE  *
**********

=> s protein(w)c(w)receptor

     70917 PROTEIN
   1332635 C
     32115 RECEPTOR
L1       3 PROTEIN(W)C(W)RECEPTOR

=> d l1,cit,rel,ab,1-3
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1. 5,852,171, Dec. 22, 1998, Cloning and regulation of an endothelial cell protein C/activated **protein** **C** **receptor**; Kenji Fukudome, et al., 530/350, 380 [IMAGE AVAILABLE]

US PAT NO: 5,852,171 [IMAGE AVAILABLE] L1: 1 of 3
REL-US-DATA: Division of Ser. No. 289,699, Aug. 12, 1994, Pat. No. 5,695,993.

ABSTRACT:
Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+ dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell **protein** **C** **receptor** (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

2. 5,804,392, Sep. 8, 1998, Diagnostic assays using soluble endothelial cell protein C/activated **protein** **C** **receptor**; Charles T. Esmon, et al., 435/7.1, 7.8, 975; 436/506; 530/387.1, 388.22, 389.1 [IMAGE AVAILABLE]

US PAT NO: 5,804,392 [IMAGE AVAILABLE] L1: 2 of 3

ABSTRACT:
Plasma EPCR has been isolated, characterized and shown to block cellular protein C activation and APC anticoagulant activity. Plasma EPCR appears to be about 43,000 daltons and circulates at approximately 100 ng/ml (98.4.+-.27.8 ng/ml, n=22). Plasma EPCR bound activated protein C with an affinity similar to that of recombinant soluble EPCR (Kd.sub.app approximately 30 nM), and inhibits both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage factor Xa clotting assay. Soluble plasma EPCR appears to attenuate the membrane-bound EPCR augmentation of protein C activation and the anticoagulant function of activated protein C. Soluble EPCR has also been detected in urine. Levels of soluble EPCR can rise in inflammatory disease associated with vascular injury and appear to be correlated with inflammation and disease states associated with abnormal coagulation. Since EPCR expression is restricted to larger vessels and is usually negative in cappillaries, these observations provide a mechanism for analyzing injury/stimulation of large vessel endothelial cells.

3. 5,695,993, Dec. 9, 1997, Cloning and regulation of an endothelial cell protein C/activated **protein** **C** **receptor**; Kenji Fukudome, et al., 435/325, 69.1, 320.1; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,695,993 [IMAGE AVAILABLE] L1: 3 of 3

ABSTRACT:
Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+ dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell **protein** **C** **receptor** (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

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U.S. Patent & Trademark Office LOGOFF AT 11:39:25 ON 28 APR 1999
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